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Radiation-Induced Tumors in Irradiated Stage I Testicular Seminoma: Results of a 25-Year Follow-Up (1968–1993)

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Background and Objectives: Testicular seminoma is a very radiosensitive and curable cancer, with survival rates following radiation therapy within the range of 90–98% without apparent severe side effects. However, long-term survival following exposure to moderate-dose radiation therapy can result in radiation-induced tumors.
Methods: The incidence of radiation-induced tumors was determined in 81 irradiated stage I testicular seminoma patients treated at the Northern Israel Oncology Center (NIOC) from 1968 through 1993.
Results: Three (4%) patients developed second cancers within the high-dose volume. Indeed, those patients received a higher than usual dose to the para-aortic and pelvic regions. One patient, who developed inoperable pancreatic carcinoma, was treated with ''hockey stick'' field and mediastinal irradiation, plus, as a result of relapses, multiple cisplatin and VP-16 based regimens.
Conclusions: The elimination of causative factors through lower total doses and field size reduction may reduce the, albeit very low, incidence of radiation-induced cancer in cured testicular seminoma.
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KEY WORDS: **testicular seminoma; stage I; radiotherapy; induced tumors**

INTRODUCTION

Early testicular seminoma is a very radiosensitive tumor with survival rates of 90–98% with no apparent severe acute or late side effects [1]. Although extensive literature suggests increasing cancer induction following exposure to low- and moderate-dose radiation therapy, the real risk has been difficult to document. Owing to the long life expectancy of irradiated early seminoma patients, this problem may increase in the future [2,3]. Our experience with radiation-induced cancer in irradiated stage I seminoma is retrospectively analyzed here.

PATIENTS AND METHODS

From 1968 through 1993, 81 patients with stage I testicular seminoma were referred to the Northern Israel Oncology Center for radiation therapy and follow-up. All patients were referred after orchiectomy and full pretreatment evaluation, including hematological and chemistry analyses, chest radiograph and bipedal lymphangiography; since 1980, tumor marker assessment (serum β-human choriogonadotrophin and α-fetoprotein) and computerized tomography of the upper/lower abdomen and lungs have become routine. Radiation techniques have been described in detail elsewhere [1].

Since 1980, the dosage to the infradiaphragmatic re-

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TABLE I. Distribution of Radiation-Induced Primaries, Treatment Modalities, and Outcome

Patient no.	Site of secondary tumor	Latency interval from seminoma (mo)	Total dose (Gy)	Daily fraction (cGy)	Treatment modality	Current status
1	Transitional cell carcinoma of urinary bladder	96	40	180	Thio-tepa instillation, fulgaration	Alive with minimal disease
2	Adenocarcinoma of sigmoid colon	12	35	180	Surgery	Dead (due to liver metastases)
3	Locally advanced pancreas carcinoma	168	26	200	Palliative care[a]	Dead (due to disease progression)

[a]Following para-aortic and pelvic irradiation, this patient developed mediastinal lymphadenopathy and lung metastases. On subsequent cisplatin-based chemotherapy and mediastinal irradiation, he entered complete remission for 12 years.

gion has been 26 Gy, with a daily fractionation of 2.0 Gy. Patients with a history of herniorrhaphy or orchiectomy received whole pelvis irradiation. The involved scrotal sac was included in the radiation field in patients who had a transscrotal approach or when the tumor was found to have infiltrated deep testicular structures.

The mean follow-up time was 150 months (range, 9–348). The evaluation of radiation-induced cancers was based on information obtained from patients' records.

RESULTS

Three (4%) patients developed radiation-induced second primary cancer (SPC), according to established criteria proposed by Cahan et al. [4]. The mean time for development of radiation-induced SPC was 92 months (range, 12–168). Patients Nos. 1 and 2, treated in the mid-1970s, received a total dose of 40 and 35 Gy, respectively, in daily fractions of 180 cGy. Patient No. 3, treated in 1980, received a total dose of 26 Gy and a daily fraction of 180 cGy (Table I). All SPC developed within the irradiated volume. None of the patients who developed second cancers had risk factors, such as heavy smoking, family history, bladder or colon polyposis, long-standing ulcerative colitis, or urinary bladder infections. Statistically, the incidence rate of a second cancer amongst our irradiated patients was relatively high when compared to the age-adjusted population in the Israel Cancer Registry [5,6]. For colon and bladder carcinoma, the expected rate in the standard age group population, as drawn from the Israel Cancer Registry, was calculated at 18.8. The actual cancer rate for the same age group [at the time of the diagnosis of the second primary cancer in our registered patients], and the actual rate of cancer for the same age group was 26/100,000 for bladder and colon cancers and 24/100,000 for pancreatic carcinoma. The ratio between the expected and the actual rates for the colon and bladder cancers was 1/333 and for pancreatic cancer, 1/500.

Patient No. 3 was treated with mediastinal irradiation and chemotherapy due to lung and mediastinal failure. He received four cycles of cisplatin, bleomycin, and vinblastine combination (Einhorn regimen [7]) and was later salvaged with three cycles of a cisplatin/VP-16 (etoposide) regimen. The cumulative VP-16 dose reached 900 mg/m^2.

DISCUSSION

An increased cancer incidence after exposure to ionizing radiation is well documented; nevertheless, the precise relationship between total radiation dose alone and radiation-induced secondary cancer (SC) is unknown. Factors such as total (including scatter) dose, dose rate, pattern of application, and radiation quality are also important. Host age at time of exposure, genetic constitution and immunodeficiency state should be taken into consideration [8,9].

Radiation therapy applied strictly to the infradiaphragmatic field will reach medially located organs, such as stomach, colon, pancreas and urinary bladder. The major Danish [2,10], Norwegian [11], and Connecticut [12] studies have shown an increasing rate of radiation therapy-induced gastrointestinal (particularly gastric carcinoma) and pancreatic cancer, which has proved to be statistically significant. However, all these statistics emerge from an era when high doses (30–45 Gy) were applied. Since lower doses of radiation therapy (25 Gy) are now used to treat seminoma, the gastrointestinal carcinoma risk should decrease.

Although a clear increased frequency of radiation-induced gastrointestinal (stomach, pancreas) and genitourinary (bladder) tract SC has been demonstrated, it is difficult to draw definitive conclusions from various series. Loss of specific and stratified clinical and radiotherapeutic data, individualized factors and the general consensus that seminoma patients have, in general, a relatively increased risk of SC regardless of previous radiation therapy, preclude meaningful analysis.

Concerning our patient No. 3 (Table I), the location of his pancreatic body carcinoma may coincide with the junctional area where the superior borders of the para-aortic field and the inferior borders of the mediastinum overlapped at depth, even with gapping on the body surface. Current modern techniques and meticulous planning may prevent significant overlap between adjacent

fields. Chemotherapy alone or in combination with extensive-field radiation therapy, is known to induce SC, mainly in malignant lymphoma. In addition to alkylating agents, high cumulative doses of etoposide have proved carcinogenic [3,13]. High-volume radiation therapy can also lower the threshold for cancer induction. All these factors should be included in treatment planning for early-stage seminoma patients.

In conclusion, the absolute number of radiation-induced SC among seminoma patients is generally low but, even so, the risk of developing such neoplasms should be kept in mind during long-term follow-up.

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